# Relation between Vitamin B12 Levels and Smell Affection in COVID-19 Patients

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## Abstract

**Introduction** Olfactory and gustative alterations are frequent in the initial stages of the COVID-19 infection. Vitamin B12 deficiency has been linked to olfactory dysfunction.

**Objective** The present study aimed to assess the relationship between vitamin B12 levels and smell affection in COVID-19 patients.

**Methods** The present study included 201 laboratory-confirmed COVID-19 patients. Smell affection was assessed using self-rated olfactory function. Serum vitamin B12 levels were assessed using commercial enzyme-linked immunosorbent assay (ELISA) kits.

**Results** According to the smell function assessment, the patients were classified into three categories: normal osmesis ($n = 77$), hyposmia ($n = 49$), and anosmia ($n = 75$) (►**Fig. 1**). Four weeks later, 195 patients (97.0%) had their normal smell function restored. The remainder 6 patients included 4 anosmic and 2 hyposmic patients. Patients with hyposmia or anosmia had significantly lower vitamin B12 levels when compared with patients with normal osmesis (median [IQR]: 363.0 [198.0–539.0] versus 337.0 [175.0–467.0] and 491.0 [364.5–584.5] pg/ml, respectively, $p < 0.001$).

**Conclusion** Vitamin B12 appears to have some contribution to smell affection in patients with COVID-19 infection.

**Keywords**
- COVID-19
- vitamin B12
- olfactory dysfunction

## Introduction

In December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially known as the 2019 novel coronavirus (2019-nCoV), started in China in Wuhan. Since then, this novel virus, also named as coronavirus disease 2019 (COVID-19), has crossed all countries' borders with dramatic spread all over the world until the World Health Organization (WHO) defined it as a pandemic disease on March 11, 2020.[1]

The novel COVID-19 is presented mainly by lower respiratory tract-related manifestations such as fever, cough, dyspnea, and chest tightness that could progress quickly to acute respiratory distress syndrome (ARDS).[2] However, COVID-19 also leads to different upper respiratory tract-related manifestations comprising sore throat, smell dysfunction, and nasal congestion.[3] The olfactory and gustative alterations are frequent in the initial stages of the infection.[2–5]

Of note, a wide variation has been reported between Chinese and European studies regarding the prevalence of taste and smell affection. In one Chinese study, anosmia and ageusia were reported in 5.1% and 5.6% of patients,

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respectively.[6] In contrast, the frequency of taste and smell disorders in European studies ranged between 19.4% and 88%.[2–5]

Vitamin B-12 deficiency is expected to result in low serum or plasma concentrations of total vitamin B-12 and holotranscobalamin, accompanied by high methylmalonic acid (MMA) and total plasma homocysteine (tHcy).[7] Severe vitamin B-12 deficiency is characterized clinically by megaloblastic anemia and neurodegenerative changes of the central and peripheral systems. Neurological effects may include cognitive impairment, peripheral neuropathy, subacute combined degeneration of the spinal cord, and psychiatric disorders.[8–10]

The present study aimed to assess the relation between vitamin B12 levels and smell affection in COVID-19 patients.

## Methods

The present prospective study was conducted at a private hospital at the **BLINDED FOR REVIEW PROCESS** between May 2020 and June 2021. The study protocol was approved by the local ethics committee of **BLINDED FOR REVIEW PROCESS**, and all patients signed an informed consent form before participation. The study included 201 COVID-19 patients with positive reverse-transcriptase polymerase chain reaction (RT-PCR) test of a nasopharyngeal swab. Patients were excluded from the study if they had history of smell dysfunction or nasopharyngeal or neurological disorders that may affect smell function and were subjected to careful history taking, thorough clinical examination and standard laboratory assessment.

The COVID-19 severity was assessed using the Infectious Diseases Society of America/American Thoracic Society (-IDSA/ATS) criteria. Patients were classified to have severe disease if they had $\geq 1$ major criterion (1. septic shock with need for vasopressors or 2. invasive mechanical ventilation) or $\geq 3$ minor criteria (1. respiratory rate $\geq 30$ breaths/min., 2. $PaO_2/FiO_2$ ratio $\leq$ 250, 3. multilobar infiltrates, 4. confusion/disorientation, 5. uremia (BUN level $\geq 20$ mg/dL), 6. leukopenia as a result of infection alone (WBC count $< 4{,}000$ cells/mL), 7. thrombocytopenia (platelets count $< 100{,}000$/mL), 8. hypothermia (core temperature $< 36°C$), 9. hypotension requiring aggressive fluid resuscitation).[11]

Smell affection was quantitively assessed using the clinical test described by Cain et al.[12] The test combines threshold testing and odor identification. According to the composite score, patients were classified into five categories of functioning: normal osmesis, mild hyposmia, moderate hyposmia, severe hyposmia, and anosmia. For convenience, we classified our patients into three categories: normal osmosis, hyposmia (whatever its severity), and anosmia. Evaluation of smell function was performed at baseline and after 4 weeks of diagnosis. Serum vitamin B12 levels were assessed using commercial enzyme-linked immunosorbent assay (ELISA) kits.

Data obtained from the present study were presented as mean and standard deviation (SD) or number and percentage. Continuous variables were compared using the one-way analysis of variance (ANOVA) with posthoc LSD comparisons. The cxategorical data were compared using the chi-squared test. Correlation analysis was achieved using the Pearson correlation analysis. A receiver operator characteristic (ROC) curve analysis was used to identify diagnostic performance of investigated marker. All statistical tests were performed using the IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). A $p$-value lower than 0.05 was considered statistically significant.

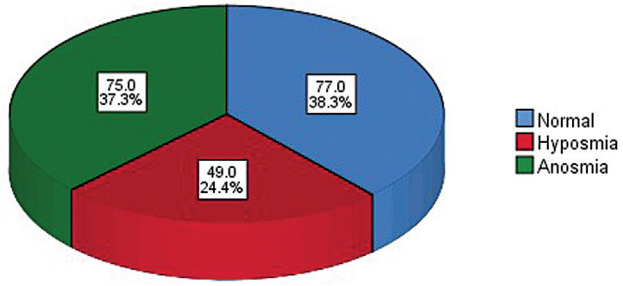


**Fig. 1** Smell affection in the studied patients.

## Results

The present study included 201 COVID-19 patients. According to smell function assessment, the patients were classified into three categories: normal osmesis ($n = 77$), hyposmia ($n = 49$), and anosmia ($n = 75$) (►**Fig. 1**). Four weeks later, 195 patients (97.0%) restored normal smell function. The remainder six patients included four anosmic and two hyposmic patients.

The comparison between patients with and without smell affection regarding the clinical and laboratory data revealed that patients with smell affection are significantly younger that patients with normal sense of smell (►**Table 1**). It was also shown that patients with hyposmia or anosmia had significantly lower vitamin B12 levels when compared with patients with normal osmesis (median interquartile range [IQR]: 363.0 [198.0–539.0] versus 337.0 [175.0–467.0] and 491.0 [364.5–584.5] pg/ml respectively, $p < 0.001$). Also, anosmic patients were found to have significantly lower vitamin B12 levels in comparison to hyposmic counterparts (►**Table 1**, ►**Fig. 2**).

The correlation analysis identified no significant correlation between vitamin B12 levels and other laboratory or clinical parameters (►**Table 2**). The ROC curve analysis showed good performance of vitamin B12 levels in identification of smell affection in COVID-19 patients (area under de curve [AUC] 95% confidence interval [95% CI]: 0.69 [0.61–0.76]) with a sensitivity and specificity of 67.7% and 63.6%, respectively (►**Fig. 3**).

## Discussion

In the present study on 201 COVID-19 patients, 124 patients (61.7%) had some degree of smell affection. They comprised 49 patients (24.4%) with hyposmia and 75 patients (37.3%) with anosmia. In comparison, one study from Saudi Arabia

 

**Table 1** Clinical and laboratory findings in the studies patients ($n = 201$)

| | All patients N = 201 | Normal osmesis N = 77 | Hyposmia N = 49 | Anosmia N = 75 | *P*-value |
|---|---|---|---|---|---|
| Age (years) median (IQR) | 31.0 (27.0- 36.0) | 33.0 (28.0–39.0) | 32.0 (28.5–38.0) | 30.0 (26.0–33.0) | 0.003 |
| Male/female n | 132/69 | 47/30 | 35/14 | 50/25 | 0.48 |
| **Covid-19 severity** n (%) | | | | | |
| Mild | 30 (14.9) | 65 (84.4) | 38 (77.6) | 68 (90.7) | 0.13 |
| Severe | 171 (85.1) | 12 (15.6) | 11 (22.4) | 7 (9.3) | |
| **Laboratory findings** median (IQR) | | | | | |
| Hb (gm/dL) | 13.0 (12.0–14.0) | 12.8 (11.8–14.0) | 13.0 (11.5–14.2) | 13.2 (12.0–14.0) | 0.27 |
| WBCs (× 103/mL) | 6.5 (4.5- 10.0) | 6.5 (4.0–10.0) | 6.0 (4.6–10.7) | 7.0 (4.5–10.0) | 0.44 |
| Platelets (× 103/mL) | 212.0 (162.5- 260.0) | 200.0 (139.5–250.0) | 200.0 (160.0–239.5) | 215.0 (180.0–259.0) | 0.17 |
| CRP (mg/dL) | 88.0 (44.5- 126.5) | 91.0 (41.0–145.5) | 93.0 (50.5–122.5) | 75.0 (41.0–118.0) | 0.42 |
| Procalcitonin (µg/L) | 0.1 (0.08- 0.2) | 0.1 (0.1–0.2) | 0.15 (0.08–0.2) | 0.1 (0.08–0.2) | 0.96 |
| LDH (U/L) | 614.0 (414.0- 908.0) | 527.0 (385.5–922.5) | 621.0 (454.5–911.5) | 618.0 (431.0–831.0) | 0.38 |
| Ferritin (µg/L) | 663.0 (442.0- 1,456.5) | 648.0 (408.5–1,549.0) | 800.0 (416.0–1,598.5) | 713.0 (507.0–1,324.0) | 0.65 |
| PT (sec.) | 13.9 (13.0–15.8) | 14.3 (13.2–15.8) | 14.8 (13.3–16.7) | 14.5 (13.0–16.0) | 0.36 |
| APTT (sec.) | 34.0 (30.0–42.0) | 35.0 (31.0–40.5) | 36.0 (32.0–45.5) | 33.0 (30.0–44.0) | 0.27 |
| D-dimer (ng/mL) | 1162.0 (746.5- 2,122.0) | 978.0 (732.0–2,122.0) | 1290.0 (810.0–2,549.0) | 980.0 (750.0–1,750.0) | 0.35 |
| Fibrinogen (gm/dL) | 3.7 (3.0- 4.8) | 3.7 (3.1–4.7) | 4.1 (3.0–5.2) | 3.5 (3.0–4.5) | 0.23 |
| Creatinine (mg/dL) | 1.1 (0.8- 1.3) | 1.0 (0.9–1.3) | 0.9 (0.9–1.25) | 0.9 (0.8–1.3) | 0.1 |
| Urea (mg/dL) | 50.0 (38.0–76.0) | 51.0 (38.0–76.5) | 56.0 (41.0–80.0) | 45.0 (37.0–72.0) | 0.42 |
| Albumin (gm/dL) | 3.2 (3.0- 4.0) | 3.5 (3.0–3.9) | 3.5 (3.1–3.8) | 3.5 (3.1–4.0) | 0.88 |
| AST (U/L) | 45.0 (29.0–72.5) | 47.0 (34.5–76.0) | 41.0 (28.0–76.0) | 42.0 (27.0–67.0) | 0.19 |
| ALT (U/L) | 51.0 (34.0- 80.0) | 59.0 (37.0–81.0) | 48.0 (33.0–80.0) | 44.0 (26.0–76.0) | 0.08 |
| O2 saturation (%) | 90.0 (80.0- 95.0) | 92.0 (80.0–95.0) | 90.0 (80.0–94.0) | 92.0 (85.0–95.0) | 0.07 |
| Vitamin B12 (pg/mL) | 403.0 (212.0- 544.5) | 491.0 (364.5–584.5) | 363.0 (198.0–539.0) | 337.0 (175.0–467.0) | < 0.001 |

Abbreviations: aPTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, c-reactive protein; Hb, hemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; PT, prothrombin time; WBCs, white blood cells.

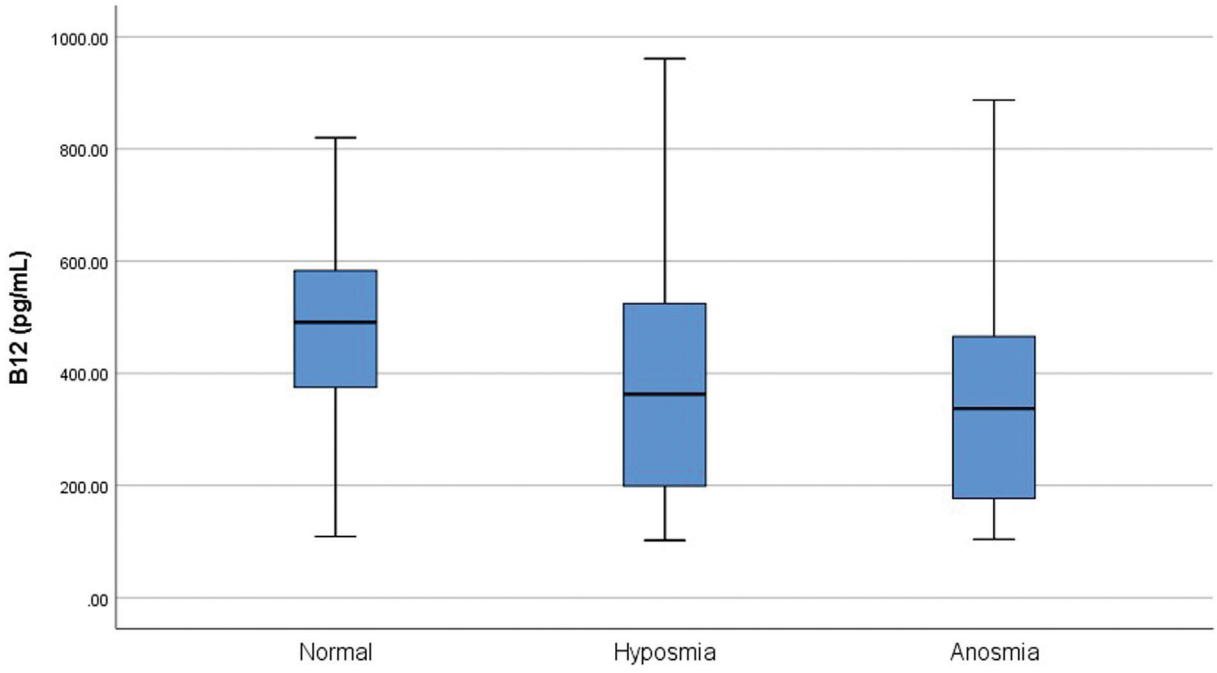


**Fig. 2** Vitamin B12 levels in the studied patients.

 

**Table 2** Correlation between vitamin B12 levels and the clinical and laboratory data

| | Vitamin B12 | |
|---|---|---|
| Age | 0.12 | 0.17 |
| Hb | 0.04 | 0.61 |
| WBCs | -0.07 | 0.35 |
| Platelets | 0.09 | 0.19 |
| CRP | 0.04 | 0.56 |
| Procalcitonin | 0.03 | 0.71 |
| LDH | −0.03 | 0.67 |
| Ferritin | −0.04 | 0.6 |
| PT | −0.04 | 0.58 |
| APTT | 0.02 | 0.82 |
| D-dimer | −0.03 | 0.7 |
| Fibrinogen | 0.11 | 0.06 |
| Creatinine | 0.14 | 0.056 |
| Urea | 0.06 | 0.41 |
| Albumin | 0.1 | 0.08 |
| AST | −0.08 | 0.26 |
| ALT | 0.11 | 0.07 |
| O2 saturation | −0.07 | 0.27 |

Abbreviations: ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CRP, c-reactive protein; LDH, lactate dehydrogenase; Hb, hemoglobin; O2, oxygen; PT, prothrombin time; WBCs, white blood cells.

noted that olfactory dysfunction was reported by 53% of COVID-19 patients, of which 32.7% were anosmic and 20.3% were hyposmic.[13] In another study, anosmia was diagnosed in 44.0% of 500 COVID-19 patients from the United Arab Emirates,[14] while anosmia was reported in 67.0% of 288 Brazilian COVID-19 patients.[15] One large meta-analysis including data from 107 studies and 32,142 COVID-19 patients found that anosmia was reported in 12,038 patients with a prevalence of 38.2% (95% CI: 36.5%, 47.2%).[16] This variation may be explained by the different tools used for diagnosis of olfactory dysfunction in different studies. In addition, other clinical or genetic factors may be involved.

Four weeks later, 195 patients (97.0%) had their normal smell function resotred. The remainder six patients included four anosmic and two hyposmic patients. In the study of Babaei et al.,[17] 88.5% of patients had their sense of smell restored by 4 weeks, while in the study of Kumar et al.,[18] 97.0% of patients recovered it within 2 weeks.

Interestingly, the present study found that patients with smell affection were significantly younger than patients with normal smell, which is in line with the former study of Mubaraki et al.[13]

In this study, we assessed the relation between vitamin B12 levels and smell affection scores in COVID-19 patients. In the first and 4 weeks, groups with higher vitamin B12 levels had significantly better self-rated smell affection scores.

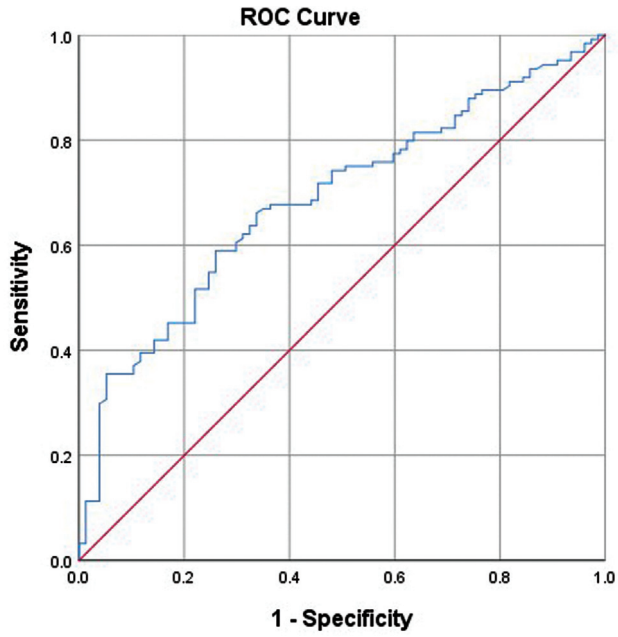


**Fig. 3** Receiver operating characteristics curve for vitamin B12 in detection of smell affection.

The association between vitamin B12 deficiency and smell affection was previously reported. The study of Derin et al.[19] showed a relation between vitamin B12 deficiency and olfactory dysfunction. Interestingly, one recent report recognized good response of COVID-19 patients with olfactory affection to vitamin B12 supplementation.[20]

The mechanisms explaining the role of vitamin B12 in olfactory dysfunction remain to be elucidated. However, the main suggested mechanism is olfactory neuronal toxicity caused by elevated homocysteine levels due to inefficient methylation of homocysteine into methionine in patients with vitamin B12 deficiency.[21,22]

## Conclusion

In conclusion, vitamin B12 appears to have some contribution to smell affection in patients with COVID-19 infection. The findings of the present study may have significant clinical implications, particularly in patients with long-term post-COVID-19 infection. The assessment of vitamin B12 levels in those patients may provide a clue for appropriate treatment. However, the value of vitamin B12 supplementation as a therapeutic strategy requires well-designed randomized clinical studies to be confirmed.

### Conflict of Interests

The authors have no conflict of interests to declare.

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